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A Review of Glomerular Diseases: Focal Segmental Glomerulosclerosis (FSG) and Minimal Change Disease (MCD)

ARTICLE INFORMATION

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ABSTRACT

Purpose: Idiopathic focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are chronic glomerulopathies which may compromise patients' quality of life, and for which there is no cure. This literature review aimed to summarize our current understanding of the pathophysiology, clinical characteristics, and best available treatment for the two conditions in order to outline a consolidated treatment protocol and identify future research considerations.
Methods: PubMed was systematically searched by a single reviewer in order to identify primary studies pertaining to the diagnosis, treatment and classification of FSGS and MCD. Additionally, a hand search of UpToDate was conducted to glean further information about the best available evidence as summarized for clinician use. Relevant information was extracted and synthesized.
Results: Primary FSGS and MCD result from distinct pathogenic mechanisms, hypothesized to involve kidney injury via immune dysregulation. Patients require a kidney biopsy for diagnostic purposes. First-line treatment involves glucocorticoids (i.e. prednisone), although patients' responsiveness may be inconsistent; second-line treatment is immunotherapy.
Conclusion: This review summarized clinically-important information about FSGS and MCD, and emphasized the need for further research in the field of clinical nephrology. Large scale trials such as the Cure Glomerulonephropathy should be conducted to gather information about the affected population.

Keywords: Focal segmental glomerulosclerosis, minimal change disease, Glomerulonephropathy, histology, review paper, clinical management

INTRODUCTION

Glomerulonephropathy (GN) refers to a broad category of inflammatory glomerular diseases, which often manifest with proteinuria, hypoalbuminemia, and edema.[1] Focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are two specific GN diseases which are the subjects of this review. Each may present idiopathically (*primary GN)* or consequent to kidney injury by systematic disease *(secondary GN)*. Diagnosis is exclusively based on histological characteristics seen on renal biopsy.[2] However, little is known about the unique pathophysiology of each condition and consequently, treatment options are rather limited. This review seeks to better understand the clinical symptoms and histologic features of FSGS and MCD, as well as to summarize the current treatment protocol for these diseases in the general adult population.

Millions of individual nephrons within each kidney process blood to produce urine through filtration, secretion, and reabsorption. The glomerular capillary

tuft mechanically filters the components of blood by size on a pressure-based system, barring individual cells and large proteins from entering the tubular nephron. Several cell types make up the glomerulus: parietal cells, capillary endothelial cells, podocytes, and mesangial cells.[1] Glomerular injury can disrupt the fine homeostatic balance maintained by this system, frequently resulting in proteinuria and hematuria as the filtration membrane is widened. Proteinuria ≥3.5 g/day, accompanied by edema, hyperlipidemia and hypoalbuminemia constitutes nephrotic syndrome (NS), an umbrella term for symptoms which are often the first indicators of FSGS or MCD.[2] These two diseases present with similar clinical features, yet each has a distinct pathogenic mechanism, necessitating separate treatment plans following pathological investigation and diagnosis.[3] Further clarifying what is known about these processes may aid clinicians in advising patients, as well as guiding further research to address unanswered questions.

METHODS

Search

Six search terms were entered into the PubMed database (September-October 2018): "(idiopathic minimal change disease) AND (biopsy)", "(idiopathic focal segmental glomerulosclerosis) AND (biopsy)", "(idiopathic minimal change glomerulonephritis) AND (treatment)", "(idiopathic focal segmental glomerulosclerosis) AND (treatment)", "(primary focal segmental glomerulosclerosis)" and "(primary minimal change disease)". The search was exhausted once duplicate results appeared frequently. Results were filtered to include studies from the last 10 years (2009-2018) and pertaining to humans only. The rationale for selecting relatively recent studies was to gather information about developing treatments on the forefront of research efforts, as well as to ensure the feasibility of the search given that a single reviewer would be responsible for screening titles. The search yield using these terms was 1380 citations. Additionally, a manual search was conducted of the UpToDate database, a resource which provides summative resources for clinicians use. This proved more relevant to information-gathering within the scope of this research paper. The following search terms were used: "minimal change disease", "idiopathic focal segmental glomerulosclerosis", "Canadian society of nephrology clinical guidelines", and "focal segmental glomerulosclerosis, minimal change disease". In order to find the seminal studies which determined clinical protocol, the citations of top search results were manually searched. These search terms were crafted based on prior knowledge of the subject and consultation with an expert clinician. Consequently, the manual search was instrumental for amassing clinically-relevant information to bolster the findings of this review.

Eligibility and Critical Appraisal

Primary studies investigating MCD and/or FSGS which were published in a peer-reviewed publication in the English language within the last 10 years (2009-2018) were included during the systematic search. Studies were excluded for irrelevance if they focused on: nephrotic syndrome generally (without making specific reference to MCD and/or FSGS in the title or abstract), secondary disease rather than idiopathic MCD/FSGS, or genetic markers of disease. Genetic factors were not assessed because the scope of this paper addresses clinically available markers of disease and treatment. Opinion pieces, abstracts, book chapters, editorials, nonhuman studies, and case reports were excluded.

Study Identification and Selection

Screening of 1380 non-duplicate titles and abstracts yielded a cohort of 234 citations to review in full. Of the 218 excluded papers: 102 were considered out of scope (i.e.: not pertinent to the questions posed in this review), 14 were specific to genetic markers of disease, 74 had an ineligible study design, and 28 addressed GN broadly rather than focusing on FSGS, MCD or both. These citations were assessed in their entirety, and 16 manuscripts were included. The methodological quality, risk of bias and precision of each study was qualitatively assessed at this point based upon the reviewer's prior experience with medical literature, and poorly-conducted studies were excluded. A formal critical appraisal using a risk of bias tool was not performed primarily due to the mix of study types being evaluated. A manual search of UpToDate was conducted to gather more specific information about treating glomerular diseases, which resulted in additional studies being included (Figure 1). All searches, screening and data extraction were completed by a single assessor. The findings of this review apply specifically to

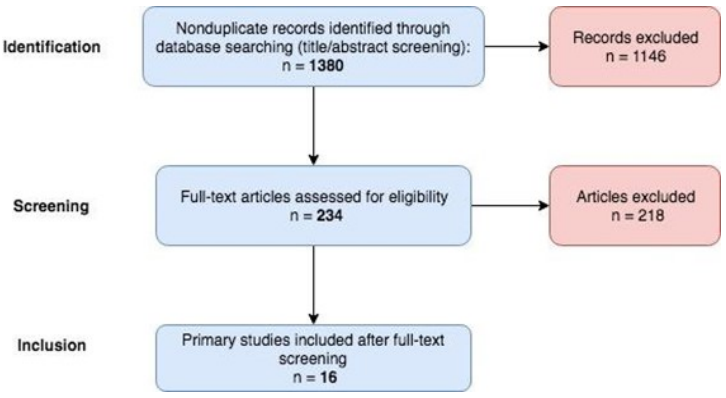


Figure 1. PRISMA flow diagram detailing the study inclusion process for this review.

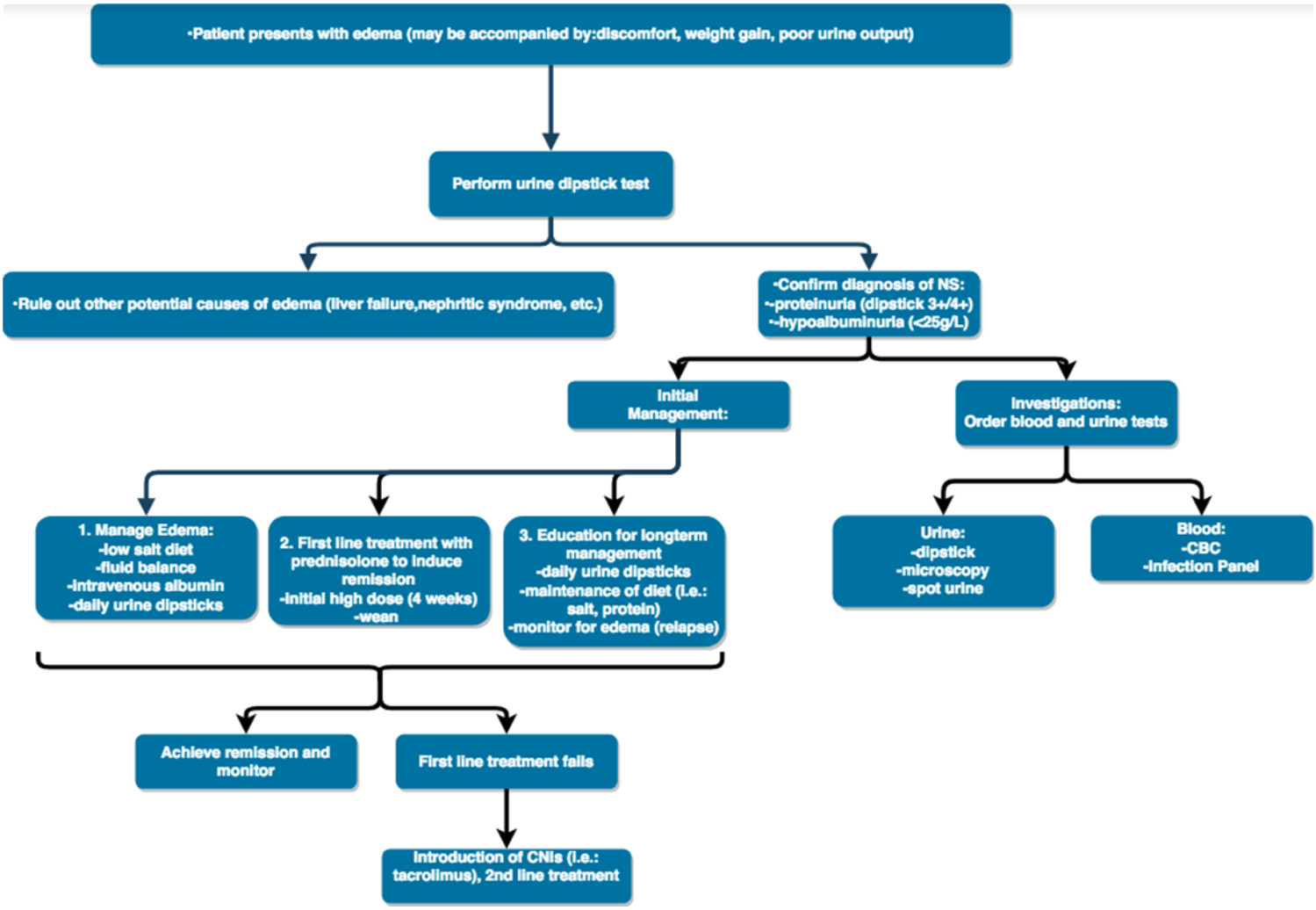


Figure 2. Standard clinical plan for diagnosis and management of patients presenting with NS.

idiopathic FSGS and MCD in adults; secondary disease warrants separate evaluation as its pathogenesis, treatment, and prognosis differ significantly from primary disease.

RESULTS

Clinical Presentation and Symptoms

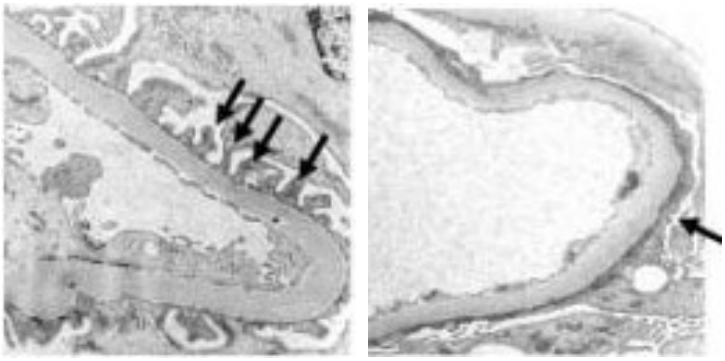
Patients suspected to have glomerular disease may present with unexplained weight gain, foamy urine and peripheral edema upon physical examination (Figure 2).[4] Frequently, they may also have a history of hypertension and in cases of MCD particularly, may have experienced an explosive onset of symptoms.[4] Bloodwork and a random urine test should be ordered at this point. Typically, lab results indicate significant proteinuria, often, in the NS range, along with hypoalbuminemia and hyperlipidemia.[2,5] This evidence may suffice to diagnose GN, however, a more specific diagnosis of FSGS, MCD, or another condition necessitates renal biopsy.

A biopsy is nearly always warranted, exempting two rare cases: i) performing the biopsy itself would result in significant harm to the patient, or the patient is unwilling to proceed, ii) glomerular injury secondary to systemic disease is strongly suspected (e.g. patients with Type II Diabetes who are experiencing diabetic nephropathy).[6,7] In general, FSGS is more common in adults and is frequently secondary, although causative factors may be difficult to determine.[8,9,10] The pathologist's determination of MCD, FSGS, or related glomerular disease is made at this point, after which treatment can be pursued. Standard treatment for both conditions includes a steroid regimen which frequently gives rise to toxic side effects and significantly compromises patients' quality of life.[2] For this reason, the renal biopsy is imperative to confirming diagnosis prior to pursuing an intensive treatment course.

Diagnostic Criteria and Biomarkers

Pathological determination of FSGS or MCD using electron microscopy is the current gold standard in GN diagnostics. Light microscopy cannot detect variation

amongst and between individual glomeruli to sufficient detail to detect podocyte effacement.[11] As its name implies, MCD is particularly difficult to diagnose given that it appears nearly identical to an undamaged specimen when examined with light microscopy – only electron microscopy suffices to view the podocyte foot process effacement (Figure 3), which causes disease symptoms.[11] Biopsy results must be interpreted in the context of clinical and laboratory findings, especially given that FSGS and MCD share a number of histologic features. The key differentiating factor between the two is the hardening of intraglomerular mesangial cells (mesangial sclerosis) which compromises capillary structure in FSGS (Figure 4).[11] However, extracted samples may be unclear (due to poor technique or damage, for example), or suffer from sampling error by failing to include an adequate number of glomeruli (at minimum, n = 23) to make a definitive diagnosis.[9, 11] These technical challenges of detecting sclerotic lesions and the upstream implications for disease treatment prompt the need for alternative diagnostic techniques at the biopsy level.

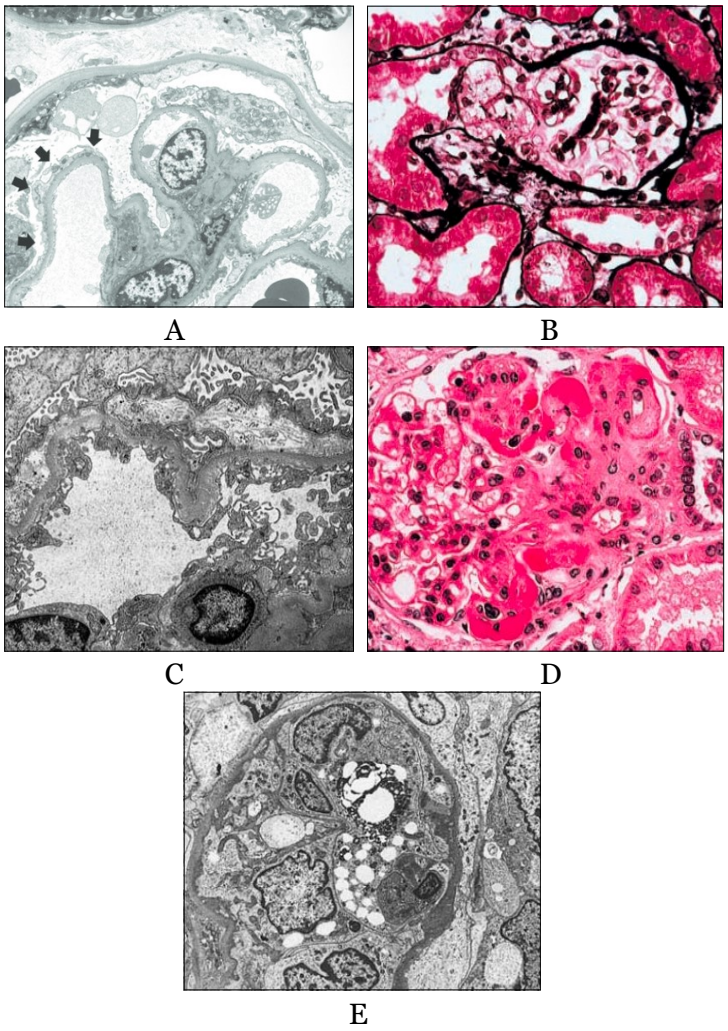


A B

Figure 3. Glomerular foot processes in a normal (a) and MCD (b) renal biopsy viewed with electron microscopy; the latter shows significant foot process effacement.[15]

The diagnosis of FSGS presents an additional challenge because the disease may be expressed as one of five pathologic subtypes which are distinct in their prognostic implications (Figure 3).[12] The variants of FSGS according to the Columbia classification system are as follows: collapsing (≥1 glomerulus showing segmental or global collapse), tip (segmental lesion on the glomerular cells nearest the proximal tubule), not otherwise specified (NOS) (segmental damage to the glomerular capillary loop), perihilar (lesions at the glomerular pole) and cellular (damage to the glomerular capillary loop with hypercellularity).[12] Pathologists should attempt to describe the subtype of FSGS when analyzing a biopsy sample because each subtype may respond differently to treatment, despite their similar clinical presentation.[12] Collapsing FSGS frequently presents with heavy proteinuria and progresses rapidly, often leading to end-stage renal disease (ESRD).[12-14] Cellular FSGS has been similarly described; this may be due either to a common causal mechanism underlying the two variants, or because of diagnostic challenges which limit our ability to detect their differences on biopsy.[12-14] Patients with collapsing and cellular variants are also more likely to be steroid-resistant upon usual treatment, further supporting the hypothesis that the two subtypes are at least closely related if not truly identical.[12, 14] The tip variant of FSGS may also demonstrate rapid disease progression, however these patients are less likely to experience CKD and/or ESRD.[13, 14] Some studies have described this variant as having a relatively less-severe prognosis, however findings did not reach statistical significance. Goals for further research should more clearly distinguish cellular versus collapsing FSGS variants, as well as plan for an adequately-powered and timed study to bolster findings related to disease prognosis.

Several studies have investigated the utility of certain biomarkers in discriminating between FSGS and MCD. Although not yet validated through extensive



A B C D E

Figure 4. Microscopy images representing FSGS variants (A) collapsing, (B) tip, (C) NOS, (D) perihilar and (E) cellular. [16]

study, cell-surface adhesion receptor CD44 shows some potential as a diagnostic marker of FSGS. CD44 is expressed on activated parietal epithelial cells (PECs), which are involved in the formation of glomerular sclerotic lesions in FSGS.[11] Pathological studies conducted in 2012 and 2014, respectively, detected sclerotic lesions in the same glomerular regions as CD44 immunostaining.[3, 11] Furthermore, CD44 expression was more robust and widely-distributed in patients with advanced disease, which may inform hypotheses regarding the mechanism and temporality of FSGS incidence.[3] Other biomarkers which have shown some success in distinguishing GN diseases include malondialdehyde, an indicator of oxidative stress, and fibrinogen, a soluble glycoprotein.[8-10] Both are elevated in FSGS biopsies and reflect glomerular irritation which may result in sclerotic lesioning.[8-10] Further research involving more patients at varying stages of disease is necessary to confirm the utility of these indicators as robust markers of FSGS vs. MCD.

Disease Mechanism

GN diseases such as FSGS and MCD may develop either idiopathically or secondarily to a systemic disease or genetic condition. FSGS is more likely attributable to secondary causes in adults, which may include: HIV, obesity, other renal diseases, or sickle cell anemia.[8] The sclerotic lesions evident upon biopsy are simply a symptom of kidney injury due to an underlying pathology. MCD is more likely to result idiopathically, often presenting with a sudden onset of symptoms.[6] Infrequently, some secondary causes such as neoplasms, atopy and certain infections may create renal damage characteristic of MCD.[6] The proteinuria which distinguishes these disorders is caused by effacement of podocyte foot processes (see Figure 5), as seen on biopsy.[8] However, there is no consensus regarding the causal factors which may originally cause glomerular injury in idiopathic cases.[6]

It has become clear that primary FSGS and MCD develop from separate disease processes. There are two primary theories addressing the etiology of MCD. Firstly, increasing evidence implicating T-cells and the cell-mediated immune response has recently come to light as the injurious factor in primary MCD.[17] For example, Garin and colleagues (2015) demonstrated that MCD patients respond, albeit temporarily, to immunotherapy targeting CTLA-4, a T-cell surface receptor and CD80 inhibitor, while FSGS patients were unresponsive.[18] These findings are reinforced by independent reports of elevated urinary CD80 excretion in MCD proteinuria.[3,18] This suggests that dysregulation of the CD80 pathway within podocytes may be responsible for initiating glomerular injury in MCD. Additionally, other medications targeting the cell-mediated immune response such as cyclophosphamide have shown some efficacy in treating MCD which further lends weight to this theory.[17] The second hypothesis regarding MCD pathogenesis describes an unknown circulating glomerular permeability factor as initiating glomerular injury. Some studies have described T-cell mediated interleukins, particularly IL-13 as potential causative factors. However, the evidence for this theory is not robust and warrants further investigation.[17]

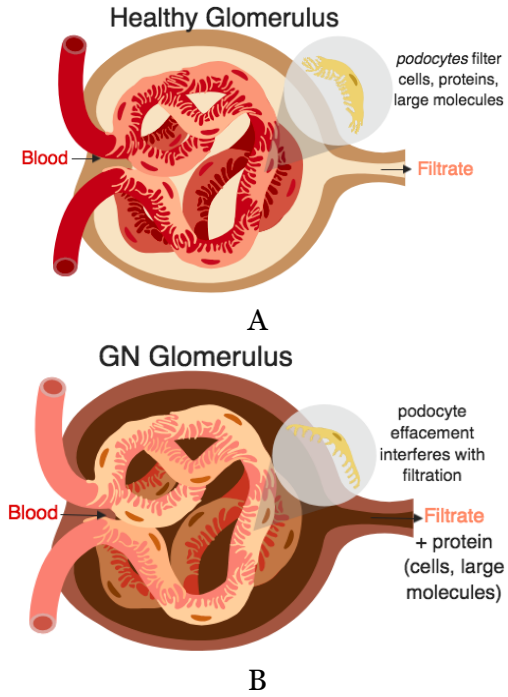


Figure 5. Illustrated glomeruli highlighting podocyte effacement in GN diseases; glomerular damage is theorized to be caused by local immune dysregulation (MCD) or by circulating permeability factors (FSGS).

Theorized mechanisms of idiopathic FSGS pathogenesis tell a similar story. Although unconfirmed, it is likely that some circulating factor is responsible for causing initial damage to PECs within the glomerulus.[18] Several pieces of evidence support the veracity of this mechanism. Firstly, animal studies have shown that injected serum from FSGS patients initiates proteinuria in otherwise healthy rats.[19] Additionally, FSGS has a relatively high rate of recurrence following remission or the receipt of a kidney transplant, which indicates the pathogenic factor is likely distal to the kidney. Soluble urokinase receptor (suPAR) has been investigated as a potential instigator of FSGS symptoms, given its functional role in adhering podocyte foot processes to the glomerular basement membrane.[18, 20] Serum suPAR levels are markedly elevated in FSGS patients, however the association is only correlational.[20] Other studies have considered microRNA (miRNA) as the circulating factor potentially responsible for FSGS. Some miRNA subtypes have been found inhibit expression of crucial podocyte-associated proteins in wildtype mice, and in human studies miRNA levels have been shown to be elevated in primary FSGS

patient glomeruli compared to controls.[21] Although the cause of injury has not yet been elucidated, the development of sclerotic lesions in FSGS is better understood:

1. Glomerular injury results in PEC activation, marked by notable cell proliferation and the production of fibrous proteins (i.e.: elevated levels of CD44 as seen on biopsy).[3, 11]
2. Local irritation results in the accumulation of matrix proteins and aggravates podocytes.[3]
3. Podocytes are terminally-differentiated cells which show low regenerative capabilities; hence they react to initial injury by hypertrophy which disrupts the filtration barrier. [3]
4. The structural changes to the glomerulus appear to produce the non-inflammatory sclerotic lesions that characterize FSGS, further underscoring the distinctness of this pathogenic mechanism from that of MCD.[3, 11, 18]

Regardless of the event responsible for initial kidney injury, both FSGS and MCD patients experience heavy proteinuria as a result of podocyte damage which compromises the glomerular filtration barrier. Consequently, large proteins from the blood are able to pass into the glomerular duct system. The excretion of protein in the urine contributes to: hypoalbuminemia (loss of albumin from the blood), edema, foamy urine (high protein content lowers liquid surface tension) and abnormal lipid metabolism (hyperlipidemia triggered by a decrease in blood oncotic pressure). [2, 4, 22] There is evidence that symptoms are reversible upon efficient diagnosis and treatment of disease.[22]

Treatment

Gold standard treatment for FSGS outlined by the International Society of Nephrology consists of high-dose glucocorticoid medication (e.g. prednisone, prednisolone) tapered after initial response.[7, 23] Patients with secondary FSGS or those with very low-grade proteinuria are not treated with steroids; conservative options including blood-pressure management through pharmaceuticals and lifestyle modifications are pursued as first-line treatment in this population. To date, this is the only routine proven efficacious by randomized-controlled trial data for the treatment of primary FSGS patients.[7] However, not all patients are responsive to prednisone and relapse rates - especially for FSGS - are high.[7, 24] What follows is a discussion of current clinical management followed by an introduction to recent findings in exploratory treatments for FSGS, then MCD.

Idiopathic FSGS is typically treated initially with glucocorticoids if patients demonstrate NS symptoms, which may be able to achieve remission with prolonged use.[7, 19, 23] Other immunosuppressants may also be used rather than prednisone/prednisolone. While glucocorticoid dose tapering is often effective, certain patients may demonstrate steroid-resistance or steroid -dependence during this phase of treatment.[19] Steroid-dependent idiopathic FSGS patients are those who relapse either while receiving, or soon after stopping glucocorticoid treatment. Conversely, steroid-resistant FSGS constitutes patients who fail to respond at all to initial treatment. Both groups who are ineffectively treated with glucocorticoids are subsequently treated with second-line therapy, which includes calcineurin-inhibitor drugs (CNIs).[19]

CNIs such as tacrolimus and cyclosporine A (CsA) have been thoroughly investigated for their efficacy in addressing the autoimmune dysregulation underlying FSGS, either in combination with low-dose prednisone or alone. Gorsane and colleagues (2016) retrospectively analyzed 23 patients with idiopathic FSGS, concluding that CsA was effective at achieving complete or partial remission in 57% of patients after approximately one year of treatment, although some nephrotoxic side effects were noted.[7] Similarly, tacrolimus has proved efficacious in the treatment of primary FSGS with estimated remission rates of approximately 60% reported.[19, 25] Studies investigating tacrolimus also report a relatively low incidence of adverse effects, the most severe of which seemed to be diarrhea and/or worsened hypertension in some patients (approximately 12%). [25, 26]

In some cases, second-line treatment may also prove ineffective, prompting clinicians to explore other treatment options which may only be supported by low or mid-level evidence. Immunosuppressants such as adrenocorticotropic hormone (ACTH) gel and similar analogues have been used with moderate success in treating some GN cases, particularly in patients with membranous nephropathy.[27, 28] Investigators seeking to evaluate its utility in treating FSGS have reported complete or partial remission in approximately 30% of patients treated with biweekly subcutaneous ACTH injections.[27] Furthermore, multiple studies of ACTH for steroid-unresponsive idiopathic FSGS patients have been plagued by high attrition and a significant incidence of adverse effects as a result of treatment.[27, 28] Despite trends towards remission of proteinuria demonstrated in these studies, the lack of robust benefit and frequency of adverse effects associated with ACTH therapy bars it from consideration as a plausible second-line treatment currently. Furthermore, ACTH therapy is extremely expensive, which creates a financial barrier to using it in exploratory or clinical settings. Other treatments options are also being explored. For example, the success of CNIs led Cho et. al to investigate the efficacy of sirolimus, a molecule with a similar structure but different immune target than tacrolimus (mammalian target of rapamycin, rather than calcineurin phosphatase) in treating FSGS.[29]

Their case-series of 6 patients was stopped early for safety reasons after 5 patients experienced severe adverse effects including worsened proteinuria.[29] It is clear that better treatment options are needed beyond first-line steroid treatment for idiopathic FSGS.

Initial management for MCD is often targeted towards management of hypertension and edema in addition resolving glomerular injury using immunosuppressant medication.[30] Patients are typically advised to follow a low-salt diet and potentially prescribed an antihypertensive medication along with glucocorticoid therapy.[30] Prednisone or prednisolone are generally very effective in achieving remission of idiopathic MCD within a few months of treatment, although approximately 10% of patients are steroid-resistant.[30] In these patients, CNIs may be used as second-line therapy. Furthermore, patients who exhibit frequent relapses of MCD when treated with tapering doses of glucocorticoids are often prescribed a continuous low dose of the medication to manage symptoms, which may be combined with a CNI in some cases.[30] Currently, there are few alternative treatments available for idiopathic MCD and consequently, steroid-responsiveness is an asset. Nakayama and colleagues (2002) retrospectively studied 62 adults with biopsy-proven MCD to determine which prognostic factors, if any, influence a patient's degree of steroid-responsiveness.[31] The majority of patients (n=53) were treated with prednisolone only, while the remainder received combination treatment with a second-line immunosuppressant.[31] Late responders (remission of proteinuria <3 g/day after 8 weeks of treatment) had more severe hematuria and renal impairment at presentation, and also displayed a larger interstitial volume on biopsy.[31] Notably, there was a significant negative correlation between age of onset and frequency of relapse, meaning that younger patients tended to benefit less from the treatment and seemed at higher risk for steroid-dependence.[31] Other studies have presented similar findings; moreover, the side-effects of first-line treatment make it a less-than-ideal long-term option even if patients respond well initially.

DISCUSSION

Key Conclusions

This paper sought to summarize our current understanding of the pathogenesis, diagnosis and treatment of idiopathic FSGS and MCD respectively, and to make recommendations for future research. These two GN diseases are difficult to distinguish between and consequently, closely associated in clinical settings. Patients with either disease often present with nephrotic-range proteinuria and warrant a renal biopsy to specify a diagnosis. Biopsy must be performed using electron microscopy and evaluate an adequate number of glomeruli to detect any focal lesions characteristic of FSGS; otherwise the two pathologies may be easily confused to even the well-trained eye. Thus, it may be advantageous to identify biomarkers of each disease which can be tested for upon biopsy. This review found that CD44 may be a feasible and effective marker of activated PECs in FSGS but not MCD, albeit these findings are limited and not yet clinically useful. Clarification of diagnosis, including FSGS subtype, is also important for prognostic reasons and treatment planning. It is clear that FSGS and MCD each develop from unrelated initial events and thus should differ in management per patient. Disease management is standardized, but not ideal. Although the Kidney Disease Improving Global Outcomes guidelines suggest steroid therapy (frequently prednisolone) as a first-line treatment, rates of non-responsiveness, disease relapse or steroid-dependence, respectively, are high, rendering this treatment option far from ideal. Recent studies have explored other methods of treatment to varying degrees of success. For instance, CNIs such as tacrolimus have proved efficacious in achieving remission, thus recommending it as a second-line treatment option; however the long-term consequences of CNI use are yet unknown. Similarly, ACTH therapy has been recently evaluated in treating FSGS however the results are not promising, suggesting that this treatment should be refined or abandoned.

Limitations

This narrative review of the literature was limited by several factors. Firstly, the literature search, development of eligibility criteria and inclusion of papers was conducted by a single reviewer who had no particular expertise in the field of nephrology. For the sake of feasibility only one database (PubMED) was systematically searched; this was supplemented by a handsearch of UpToDate to glean more specific information. Unpublished data, gray literature and conference abstracts were not included, however the many small and inconclusive studies included makes it unlikely that the review suffered from publication bias. The majority of the included studies were relatively small, primary experiments and there was considerable heterogeneity between studies with regards to geographic location, patient population, methodology and even results. Thus, readers should proceed with caution when assessing the conclusions made in this paper and use it as general information rather than as a decision-making tool. This paper's research question was rather unfocused and consequently this paper addressed FSGS and MCD as a broad overview rather than answering clinically-relevant questions. Finally, much of the included research was purely qualitative and/or would have contributed to significant heterogeneity, which discouraged the pooling of data to esti-

mate overall findings. For these reasons the results of this study should be used as background information to learn about FSGS and MCD, and perhaps to inform the development of future research questions.

This review sought to provide a fundamental overview of the rare glomerular diseases FSGS and MCD. It touched upon clinical signs and symptoms, underlying pathogenic mechanisms, as well as ongoing research regarding biomarkers of the diseases and treatment options. Key findings include the affirmation that FSGS and MCD stem from separate disease processes despite their similar presentation and that certain biomarkers may help to distinguish between the two pathologies on renal biopsy. The evidence and productivity of research in this subfield of nephrology is relatively weak. Consequently, it would be irresponsible to draw robust conclusions from the findings of this paper. It has become sufficiently clear that bigger and better studies are needed to learn about GN diseases. Cure Glomerulonephropathy is an example of one such study which hopes to gather enough data to learn about nephropathies in the general population and ultimately lead to improved patient outcomes (see *Next Steps, below).*

Next Steps: Cure Glomerulonephropathy (CureGN)

The findings of this paper serve to provide a basic overview of recent literature published on the topic of FSGS and MCD. More importantly, it is able to point out glaring gaps in our knowledge of these diseases such that effective research can be done towards improving patient outcomes. CureGN is an ongoing multi-centre, cohort study which recognized the need to gather more information about GN.[32] It began enrolling patients in December, 2014 and aims to include n=2400 adult and pediatric patients diagnosed with idiopathic GN diseases including FSGS and MCD. As of August 3, 2018, 2202 patients were enrolled, an impressive feat considering the relative rareness of primary GN diseases in the general population (estimated period prevalence 2007-2011 in the US population= 306/100 000 persons).[32, 33] The study aims to establish a longitudinal cohort of GN patients, collecting biospecimens and patient-reported outcome information over a 4 year period. Concurrent to a literature search, the authors of this paper gathered anecdotal information about current research in GN diseases by assisting with data collection for the CureGN study under the supervision of Dr. P. Boll and Martin Romano at Credit Valley Hospital in Mississauga, Ontario. The study requires participants to undergo an initial diagnostic biopsy within 5 years of enrollment. The sample is reviewed by a pathologist, undergoes both electron microscopy and immunofluorescent assessment, and is stored at a biorepository site in Michigan. Following enrollment, patients are assessed 4 times per year; blood samples and urine specimens are procured at each visit if possible.[32] Outcomes of the study are broad and varied within the following categories: epidemiology (including demographics, medical history, etc.), biomarkers (renal biopsy, blood and urine samples), genetics (analysis of blood and urine samples) and patient-reported outcomes (quality of life).[32] The miscellaneous nature of CureGN's target outcomes reflects the severe lack of concise information regarding these diseases in the literature currently. The study aims to standardize data-collection methodology amongst a large sample which is representative of the general population, hoping to spur more specific ancillary studies derived from this initial database. The cacophony of fragile and/or conflicting results from small, observational studies renders research progress slow and unproductive in the field of GN disease. Hence, this multicentre trial is a necessary first step towards providing a more robust characterization of the patient population and leading the way to more personalized treatment options.

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APPENDIX

Table 1. Diagnostic criteria for various disease states amongst GN patients.[34-36]

	24-hour urine protein	Albumin	Clinical Signs	Other common findings
NS Diagnosis	3.5g	<25g/L	• Peripheral edema • Abdominal cramps • Dizziness • Thrombosis • Peripheral hypoperfusion	• Hyperlipidemia (>350mg/dL) • Microscopic hematuria
Complete Remission	<0.3g		• Diminished edema • Large quantities of urine produced	
Partial Remission	0.3-3.5g		• Diminished edema • Large quantities of urine produced	
Relapse	3.5g/day for 3 consecutive days		• Peripheral edema • Abdominal cramps • Dizziness • Thrombosis • Peripheral hypoperfusion	• Hyperlipidemia • Microscopic hematuria